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| EXAMINER | |
|---|---|
| KIM, YOUNG J | |

| ART UNIT | PAPER NUMBER |
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| 1637 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

mailroom@bskb.com

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/060,301 | NAKAMURA ET AL. | |
| | Examiner | Art Unit | |
| | Young J. Kim | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-3 and 5-11* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 5-11* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

The present Office Action is responsive to the Amendment received on July 17, 2008.

### *Preliminary Remark*

Claim 4 is canceled.

Claim 11 is new.

Claims 1-3 and 5-11 are pending and are under prosecution herein.

### *Claim Rejections - 35 USC § 112*

The new matter rejection of claims 5-8 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, made in the Office Action mailed on January 18, 2008 is withdrawn in view of the Amendment received on July 17, 2008, removing the new matter.

### *Rejection, New Grounds – Necessitated by Amendment*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 11 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a New Matter Rejection.

Claim 11 is drawn to a method of simultaneously amplifying up to 100 nucleotide sequences, each nucleotide sequences comprising at least one SNP using 40 ng of genomic DNA and a plurality of primer pairs.

This claim literally reads on amplifying a single SNP from 40 ng genomic DNA using a plurality of same primer pairs.

The instant application does not contemplate this embodiment.

***Claim Rejections - 35 USC § 103 - Maintained***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1, 3, 5, 7, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082), made in the Office Action mailed on January 28, 2008 is maintained for the reasons of record.

**In addition,** claim 11 is rejected herein as being **necessitated by Amendment**.

Applicants' arguments presented in the Amendment received on October 31, 2007 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

Preliminarily, the full-breadth of the claims are construed as follows.

The limitation imposed by the phrase, "genomic DNA whose amount is 10-40 ng per 100 sites," embodies a range of 0.1 ng to 0.4 ng per a single SNP site. Thus, the method requires at least 0.2 ng of genomic DNA in claims 1 and 3 which recite the step of simultaneously amplifying "at least two sites," and at least 0.1 ng of genomic DNA in claims 5-8 which recite the step of simultaneously amplifying one or more sites."

Additionally, claims 7 and 8 does not require that the 50 pairs of more primer be primer pairs which amplifies different SNP sites. Thus, employing at least 50 pairs of the primer pairs which amplify a single SNP site (i.e., having the same sequences) would necessary meet this limitation.

The Rejection:

Mein et al. disclose a method of coupling multiplex amplification of polymorphic loci from a genomic DNA, followed by detecting the single nucleotide polymorphisms by Invader® assay method (Abstract, page 331, 2nd column).

Mein et al. disclose that 36 SNPs sites were amplified (page 331, 2nd column), employing 10 ng of starting DNA. Mein et al. are silent as to how many SNP sites were simultaneously amplified using the 10 ng of starting DNA.

Hence, Mein et al. do not employ 50 or more primer pairs in their method nor genomic DNA whose amount is 10-40 ng per 100 sites.

Wang et al. disclose a method of detecting SNPs by first simultaneously amplifying (or multiplexing) a plurality of primer pairs, including 558 loci, necessarily including more than 50 primer sets, considering that a singe primer set amplifies a single loci (page 1080, 3rd column).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Mein et al. with the teachings Wang et al. to arrived at the claimed invention for the following reasons.

The motivation to multiplex more target sites in amplification, that is, simultaneously amplifying multiple target sites, is a well-established desire in the art. As Wang et al. put it:

> "We next sought to **decrease substantially the sample preparation required to generate large numbers of SNPs, as required to perform a genome scan. We developed a protocol based on multiplex PCR in which primer pairs from many different loci are combined in a single reaction**." (page 1080, 3rd paragraph, 1st paragraph)

Wang et al. employ 100 ng of DNA for simultaneously amplifying a plurality of loci, including 24 sets of approximately 23 loci, 12 sets of approximately 46 loci, 6 sets of approximately 92 loci (page 1080, 3rd paragraph, 1st paragraph), and a single set of 558 loci.

Therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. with the teachings of Wang et al. to arrive at simultaneously amplification involving at least 50 pairs of primers or more.

Wang et al. disclose that 12 sets of 46 loci; (46 loci being amplified simultaneously); 6 sets of 92 loci; a single set of 558 loci were amplified simultaneously (page 1080, 3rd column).

While the artisans disclose that different multiplex amplification reactions gave different percentage of loci being successfully amplified, Wang et al. explicitly discusses that it may be possible to salvage the unsuccessful assays by grouping them into additional multiplex sets or by *redesigning* the assays.

One of ordinary skill in the art at the time the invention was made would have been motivated to combine the teachings of Mein et al. and the teachings of Wang et al. to achieve

multiplex amplification involving a plurality of primers for the advantage of decreasing sample preparation (as expressed by Wang et al.), wherein the artisan would have had a reasonable expectation of success at such combination as Wang et al. clearly envisions that by redesigning, multiplexing even up to 558 loci would be achievable, through optimization.

Regarding optimization, the MPEP 2144.05(II)(A) clear that, "differences in concentrations or temperature ***will not support*** patentability of subject matter encompassed by prior art unless there is evidence indicating such concentration or temperature is critical," citing *In re Aller,* F.2d 454, 456, 105 USPQ 233, 235, (CCPA 1995). Analogously, optimizing parameters for multiplexing multiple target sites in an amplification reaction would be considered routine, as provided for by Wang et al.

In addition, based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in a 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci), with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success.

Therefore the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants state that the *prima facie* case has not been demonstrated because the combination of the teachings do not result in at least 98% successful detection have not been achieved by the artisans, but only 50% successful detection of the sites (page 6, 2nd paragraph, Response).

Preliminarily, the very last sentence of Applicants' statement found on page 6, 2nd paragraph of the Response appears to be incomplete:

"This is far from 100% success, and one of skill would recognize that optimization of the assay would not"

Applicants state that the current method is directed to both multiplex amplification by PCR and genotyping via assay and that Wang does not disclose or suggest typing after multiplex PCR where the success rate of typing is 98% and Mein does not disclose a similar success rate (page 6, 3rd paragraph, Response).

It is respectfully submitted that the rejection is based on a combination of references. Had Wang et al. or Mein et al. disclosed the entire limitation of the claims, the rejection would have been under anticipation, not under obviousness.

What is clear is that the disclosure provided for by Wang et al. reasonably demonstrated that 100 sits of SNP can be simultaneously amplified based on 10-40 ng of DNA per site. This reasoning was clearly conveyed to Applicants in the above rejection of record, but made of record again herein:

In addition, based on the fact that a single multiplex amplification involving 100 ng of DNA for amplifying 558 loci resulted in a 50% success, one of ordinary skill in the art would have had a reasonable expectation of success at employing half the number of the loci (approximately 279 loci), with the 100 ng of starting DNA (which would result in 0.36 ng per target site) with close to a 100% success.

Clearly, if one of ordinary skill in the art was capable of achieving 50% success rate of simultaneously amplifying 558 different SNP loci from 100 ng of starting DNA, one of ordinary skill in the art would have reasonable expected that multiplexing only the half of the successful loci (279 loci) based on 100 ng of starting DNA, which calculates to 0.36 ng of DNA per SNP loci.

While Applicants state that Wang et al. were capable of typing only 50% detection, this was because Applicants are referring to the success rate of the 558 simultaneous amplification. Sine only 50% of 558 loci were successfully amplified, only 50% could be Detected.

However, Applicants are not addressing the rationale which the previous Office Action provided for holding the claims obvious.

Applicants' claim is drawn to a method which first simultaneously amplifies at least two sites, of SNP using a DNA whose starting amount is 10-40 ng per 100 SNP sites. This translates to 0.1ng to 0.4 ng per SNP site.

As stated previously Wang et al. clearly demonstrated that 279 loci were capable of being simultaneously amplified based on 100 ng of starting DNA. This translates to 0.36 ng of DNA per SNP site.

Thus, it is abundantly clear that one of ordinary skill in the art would recognized that 0.36 ng of DNA per SNP site, for amplifying at least 279 SNP loci simultaneously would have been capable.

Having amplified these SNP loci, one of ordinary skill in the art would have been motivated to employ any of the known means of detecting the amplified nucleic acids which comprise the SNPs, such as that which is disclosed by Mein et al., so as to arrive at the detection.

Applicants state that there is no suggestion to use "TAQMAN or INVADER assay for detection of the polymorphisms." (page 6, bottom paragraph).

If Applicants are contending that Wang et al. must suggest explicitly suggest the use of TAQMAN or INVADER assay for typing, Applicants are reminded of *in re Oetiker*:

> In *in re Oetiker,* 977, F.2d 1443, 1448 (Fed. Cir. 1992), the court stated the following: "[T]here must be some teaching, reason, suggestion, or motivation found "in the prior art" or "in the prior art references" to make a combination to render an invention obvious within the meaning of 35 U.S.C. 103 (1998). Similar language appear in a number of opinions and if taken literally would mean that an invention cannot be held to have been obvious unless something specific in a prior art reference would lead an inventor to combine the teachings therein with another piece of prior art.

> **This restrictive understanding of the concept of obviousness is clearly wrong**…. While there must be some teaching, reason, suggestion, or motivation to combine existing elements to produce the claimed device, it is not necessary that the cited references or prior art specifically suggest making the combination…. In sum, it is off the mark for litigants to argue, as many do, that an invention cannot be held to have been obvious unless a suggestion to combine the prior art teachings is found in a specific reference."

What Applicants are contending is that one of ordinary skill in the art would not have the requisite knowledge or creativity to combine other well known detection means in the art so as to construct the presently claimed invention.

This presumption is clearly wrong.

For example, if one of ordinary skill in the art found a reference teachings which disclose a method of simultaneously amplifying 100 SNPs by using 0.36 ng of DNA per site, but detects the polymorphisms via restriction fragment length polymorphism, would that one of ordinary skill only conclude that RFLP is the sole means of SNP typing said one could use?

Contrary to Applicants' assertion, given the fact that Wang et al. clearly provide the capability to simultaneously amplify over 100 (279 loci) sites of SNPs using 0.36 ng of DNA per site, one of ordinary skill in the art would have had no doubt that that any means of detection known in the art, such as that which is disclosed by Mein et al., would have been combinable.

Applicants refer to the examiner's statement made in the previous Office Action, wherein it was stated, "[t]he position taken by the Office is more reasonable than that which is taken by Applicants" (page 7, 1st paragraph, Response).

Applicants argue that the measure of obviousness is not whether the Office is reasonable (page 7, 1st paragraph, Response).

It is respectfully submitted that Applicants' are stating the examiner's statement out of context.

The above-cited statement made by the examiner is based on the following context (found on page 7-8 of the previous Office Action).

In Applicants' arguments received on October 31, 2007, Applicants stated that rate of successful typing is not a linear function of the input DNA amount or the number of loci amplified at once, but rather, failure of the typing assays occur at least partly due to ***primer dimer formation and annealing of primers to secondary (i.e., not the target locus) sites in the genome*** (page 7, 3rd paragraph, Applicants' arguments received on October 31, 2007)

This argument was made in response to the Office's position that if 50% of 558 SNP loci were successfully amplified using 100 ng of DNA, why wouldn't one of ordinary skill in the art recognize that those successful loci (279 of them) can be 100% amplified using 100 ng DNA.

This fact was contrasted with Applicants' statement made in the instant specification, wherein Applicants state that because they discovered that a single site (SNP) can be typed (not multiplex) based on 0.1 ng of starting DNA, thousands of SNP sites can be amplified simultaneously using 0.1 ng of DNA per SNP site.

It was in this context, it was stated that the position taken by the Office (which is no position at all, but a fact) was more reasonable than that which is taken by Applicants.

Lastly, Applicants state that the claims are drawn to simultaneously amplifying up to 100 nucleotide sequences using 10-40 ng of genomic DNA (page 7, 1st paragraph, Response).

This statement is also not entirely correct.

Claim 1 is drawn to a method which "simultaneously amplifying a plurality of sequences, said plurality of sequences comprising at least two sites of SNP using DNA whose amount is 10-40 ng per 100 sites.

Clearly, claim 1 does not limit as to how many SNP sites can be simultaneously amplified, so long as the method employs 0.1-0.4 ng per SNP site, which would literally embrace simultaneous amplification of 10,000 SNP sites.

Claim 9 is also similarly not limiting to amplification of 100 sites as Applicants currently assert.

Lastly, with regard to the Nakamura Declaration, it should be noted that no Table is attached.

In addition, the unexpected result cannot be established for the claims if the experimental condition is not the same scope as that which is claimed in the instant application.

The rejection is maintained therefore.

The rejection of claims 2, 6, and 8 under 35 U.S.C. 103(a) as being unpatentable over Mein et al. (Genome Research, March 2000, vol. 10, no. 3, pages 330-343) in view of Wang et al. (Science, May 1998, vol. 280, pages 1077-1082) as applied to claims 1, 3, 5, 7, 9, 10, and 11 above, and further in view of Brooks (US 2001/0046670 A1, issued November 29, 2001, priority October 7, 1999), made in the Office Action mailed on January 28, 2008 is maintained for the reasons of record.

Applicants' arguments presented in the Amendment received on July 17, 2008 have been fully considered but they are not found persuasive for the reasons already discussed above.

The Rejection:

The teachings of Mein et al. and Wang et al. have already been discussed above.

Neither Mein et al. nor Wang et al. employ "hot start" amplification (claims 2, 6, and 8)

Brook discloses a multiplex amplification [0076] reaction which involves hot start amplification [0066].

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the teachings of Mein et al., and Wang et al. with the advantage offered by Brooks to arrive at the invention as claimed for the following reasons.

Brook clearly discusses the advantage of employing "hot start" PCR method:

"…other 'Hot Start' type PCR conditions are used to limit primer dimer artifacts as much as possible." [0066].

As one of ordinary skill in the art in the art of amplification would recognize that primer dimer artifacts are to be minimized in amplification procedures, it would have been obvious to implement this teachings into the teachings of Mein et al., and Wang et al. to arrive at the claimed invention with a reasonable expectation of success.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

## ***Conclusion***

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the

mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

### *Inquiries*

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

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/Young J. Kim/
Primary Examiner
Art Unit 1637
10/9/2008

/YJK/